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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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Mohamed Abdulkader Ibrahim

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EXAMINER

MCDOWELL, BRIAN E

ART UNIT

PAPER NUMBER

1624

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DELIVERY MODE

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PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No. bm	Applicant(s) IBRAHIM ET AL.	
	Examiner BRIAN MCDOWELL	Art Unit 1624	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 12/11/2008.
- 2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 9-18 and 30-32 is/are pending in the application.
- 4a) Of the above claim(s) 10-18 is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 9, 31 and 32 is/are rejected.
- 7) ☒ Claim(s) 30 is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
 2. ☐ Certified copies of the priority documents have been received in Application No. _____.
 3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|--|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413) |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | Paper No(s)/Mail Date. _____ |
| 3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08) | 5) <input type="checkbox"/> Notice of Informal Patent Application |
| Paper No(s)/Mail Date _____ | 6) <input type="checkbox"/> Other: _____ |

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DETAILED ACTION

Status of Claims

Claims 9-18 and 30-32 are pending in the application. Claims 1-8, 19-29, and 33-38 have been cancelled. Claims 10-18 have been withdrawn from consideration. An action on the merits of claims 9 and 30-32 is contained herein below.

Status of Election of Species

Applicant's elected specie was determined to be free of the prior art (see 103 rejection below), thus the full scope of the claims have therefore been examined.

Status of Claim Objections

Applicant's amendment of claim 32, see Remarks, filed 12/11/2008, with respect to the objection set forth in the Non-Final Office Action mailed 8/11/2008, has been fully considered and the objection has been overcome.

Status of Rejections

35 USC § 112 (2nd Paragraph)

Applicant's amendment of claim 30, see Remarks, filed 12/11/2008, with respect to the rejection set forth in the Non-Final Office Action mailed 8/11/2008, has been fully considered and the rejection has been overcome.

35 USC § 102

Applicant's cancellation of claims 1-6, see Remarks, filed 12/11/2008, with respect to the rejection set forth in the Non-Final Office Action mailed 8/11/2008, has been fully considered and the rejection has been overcome.

35 USC § 103

Applicant's arguments of claims 1-9, 30, and 31 (now claims 9, 30-32), see Remarks, filed 12/11/2008, with respect to the rejection set forth in the Non-Final Office Action mailed 8/11/2008, has been fully considered and found persuasive, thus the rejection has been overcome.

New Objections and Rejections

Claim Objections

Claim 9 is objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. Applicant is required to cancel the claim(s), or amend the claim(s) to place the claim(s) in proper dependent form, or rewrite the claim(s) in independent form. In the instant case, claim 9 depends on canceled claim 8.

Claim 30 is objected to because of the following:

A period is needed at the end of the table 3. Please correct.

Claim 30 contains non-elected subject matter (see compounds 16 and 57). The elected invention is drawn to group I, where the heterocyclic ring forms a quinazoline ring that is substituted with nitrogen at the 4-position. Please correct and take note of other compounds that are potentially embraced by this claim that do not fall within the scope of Group I.

Claim Rejections - 35 USC § 112 (2nd Paragraph)

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 9, 31, and 32 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 9 recites limitations for “variables Y and Z” in formula IV. There is insufficient antecedent basis for this limitation in the claim.

Since claims 31 and 32 depend on claim 9 they are indefinite as well.

Claim Rejections - 35 USC § 112 (1st Paragraph)

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claim 32 is rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for making salts of the claimed compounds, it does not reasonably provide enablement for making metabolites of the claimed compounds. The claim(s) contains subject matter, which was not described in the specification in such a way as to enable one skilled in the art of medicinal chemistry to use the invention. "The factors to be considered [in making an enablement rejection] have been summarized as

- a) the quantity of experimentation necessary,**
- b) the amount of direction or guidance presented,**
- c) the presence or absence of working examples,**

d) the nature of the invention,

e) the state of the prior art,

f) the relative skill of those in that art,

g) the predictability or unpredictability of the art,

h) and the breadth of the claims", *In re Rainer*, 146 USPQ 218 (1965); *In re Colianni*, 195 USPQ 150, *Ex parte Formal*, 230 USPQ 546.

a) Although attempts have been made to predict drug metabolism *de novo*, this is still an experimental science. Therefore, determining the resulting products of this process would be equally as daunting and would require a large quantity of experimentation.

b) The direction concerning metabolites is not found in the specification. Therefore, the structures of these "metabolites" must be uncertain as well.

c) There is no working example of a metabolite of a compound of the formula IV. The examiner did not find a single "metabolite" in the art in regards to compounds possessing the quinazoline core seen in formula IV.

d) The nature of the invention is 4-amino substituted quinazolines for the treatment of abnormal cell proliferation through inhibition of TIE-2.

e) Wolff (Medicinal Chemistry) summarizes the state of the prodrug art and metabolism. Wolff, Manfred E. "Burger's Medicinal Chemistry, 5ed, Part I", John Wiley & Sons, 1995, pages 975-977. Specifically, it has been noted that difficulties in metabolite kinetics arise when the prodrug is not completely biotransformed to the active "drug" (see page

975, section 8.6, first paragraph). Thus, it would be nearly impossible to determine the amount and structures of the resulting metabolites that would be formed *in vivo*.

f) One would have a Ph. D. degree and several years of industrial experience.

g) It is well established that "the scope of enablement varies inversely with the degree of unpredictability of the factors involved", and physiological activity is generally considered to be an unpredictable factor. See *In re Fisher*, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970).

h) The breadth of the claims includes all of the hundreds of thousands of compounds of formula IV in claim 9 as well as the presently unknown list of potential metabolites embraced by the claims.

MPEP 2164.01(a) states, "[a] conclusion of lack of enablement means that, based on the evidence regarding each of the above factors, the specification, at the time the application was filed, would not have taught one skilled in the art how to make and/or use the full scope of the claimed invention without undue experimentation. *In re Wright*, 999 F.2d 1557,1562, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993)." That conclusion is clearly justified here. Thus, undue experimentation will be required to determine if any particular compound of unknown structure is, in fact, a metabolite.

Nowhere in the specification are directions given for preparing the "metabolites" of the claimed compounds. Since the structures of these "metabolites " are uncertain, direction for their preparation must also be unclear.

Conclusion

No claims are allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to BRIAN MCDOWELL whose telephone number is (571)270-5755. The examiner can normally be reached on Monday-Thursday 8:30-5:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Mr. James O. Wilson can be reached 571-272-0661. The fax phone

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number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

BM

/James O. Wilson/

Supervisory Patent Examiner, Art Unit 1624